UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/568,055	09/27/2006	Aidan Doherty	6947-73362-01	3696

24197 7590 05/28/2009

KLARQUIST SPARKMAN, LLP
121 SW SALMON STREET
SUITE 1600
PORTLAND, OR 97204

EXAMINER	
HUTSON, RICHARD G	

ART UNIT	PAPER NUMBER
1652	

MAIL DATE	DELIVERY MODE
05/28/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/568,055	DOHERTY ET AL.	
	Examiner	Art Unit	
	Richard G. Hutson	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/23/2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43* is/are pending in the application.

4a) Of the above claim(s) *15-17, 24-27 and 34-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14,18-23 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/27/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's preliminary amendment of claims 2-8, 10-23, 25, 27-33 and 35-43 in the paper of 4/23/2009, is acknowledged. Claims 1-43 are still at issue and are present for examination.

Election/Restrictions

Applicant's election with traverse of Group I, Claims 1-14, 18-23 and 28-33, in the paper of 4/23/2009, is acknowledged. The traversal is on the ground(s) that Weller et al. cannot be used as prior art against this application on the basis that the subject matter of the claimed invention that is described in Weller et al. is the work of the inventors alone, thus Weller et al. does not qualify as prior art by another.

Applicants complete argument regarding the removal of Weller et al. as art is acknowledged, however is not found persuasive until the perfection of applicants submitted declaration, which is based upon the statements by all four inventors but currently only signed by three inventors.

Further, as applicant's attention is directed to the rejection below under 35 U.S.C. 102(a) over Mahajan et al. (U.S. Patent No. 5,976,806) as it relates to applicants submission of unity between the claims.

Claims 15-17, 24-27 and 34-43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper."

Applicants filing of information disclosure statement filed on 9/27/2006, is acknowledged. Those references considered have been initialed.

Specification

The disclosure is objected to because of the following informalities:

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth: The following portions of the specification list sequences which appear to meet the definition for a nucleic acid sequence, but do not have an associated SEQ ID No: Figure 12.

Appropriate correction is required.

Claim Objections

Claims 1-14, 18-23 and 28-33 are objected to because of the following informalities:

Claim 1 (2-14, 18-23 and 28-33 dependent from) recites "contacting the nucleic acid molecule with a prokaryotic DNA repair ligase polypeptide". For the purposes of advancing prosecution this recitation is interpreted as requiring the hand of man, however, in order to make such clear it is suggested that the recitation be amended such as "contacting the nucleic acid molecule with an **isolated** prokaryotic DNA repair ligase polypeptide".

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1-14, 18-23 and 28-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (claims 2-14, 18-23 and 28-33 dependent upon) is indefinite in the recitation "prokaryotic DNA repair ligase polypeptide" as it is unclear and thus indefinite as to exactly what a "prokaryotic DNA repair ligase polypeptide" is. The basis of this indefiniteness is that it is unclear as to how the recited "prokaryotic DNA repair ligase polypeptide" is different from a "prokaryotic DNA ligase polypeptide". It is unclear as to the purpose of the word "repair" and whether this somehow differentiates the ligase of the claimed method from any other prokaryotic DNA ligase". As applicants specification does not clarify those properties specific to a "prokaryotic DNA repair ligase

polypeptide", in the interest of advancing prosecution "prokaryotic DNA repair ligase polypeptide" is interpreted as "prokaryotic DNA ligase polypeptide".

Claim 5 recites the limitation "the Mt-Lig polypeptide" in claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim 5 is indefinite in the recitation "Mt-Lig polypeptide" as it is unclear as to exactly what a "Mt-Lig polypeptide" is.

Claim 8 (claims 9-14 dependent on) is indefinite in the recitation "non-compatible" in reference to nucleic acid ends. It is unclear as to exactly what a non-compatible nucleic acid end is. Applicants specification at page 7 states that "non-compatible ends" are non-complementary and therefore non-cohesive, however, it remains as to what other types of ends are also included in non-compatible". For instance, while applicants state that non-compatible ends may comprise non-complementary single stranded 5' or 3' overhang regions which do not naturally form base-pairs, it remains if applicant's definition includes ends beyond these such as blunt ends.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-14, 18-23 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-14, 18-23 and 28-33 are directed to all possible methods of modifying a nucleic acid molecule comprising contacting a nucleic acid molecule with any prokaryotic DNA repair ligase polypeptide (See also above rejection under 112 second paragraph). The specification, however, only provides those methods of ligating nucleic acid molecule ends comprising contacting that ligase isolated from Mycobacterium tuberculosis and having the amino acid sequence of database accession number CAB08492, encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these DNA repair ligase polypeptides by any identifying structural characteristics or properties other than the amino acid sequence of CAB08492, for which no predictability of structure is apparent. Further applicant's reference to the amino acid sequence of accession number CAB08492 and CAB08491 appears to be an improper incorporation by reference of essential subject matter. Given the lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-14, 18-23 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of ligating nucleic acid molecule ends comprising contacting that ligase isolated from *Mycobacterium tuberculosis* and having the amino acid sequence of database accession number CAB08492, does not reasonably provide enablement for any method of modifying a nucleic acid molecule comprising contacting the nucleic acid molecule with any prokaryotic DNA repair ligase polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-14, 18-23 and 28-33 are so broad as to encompass any method of modifying a nucleic acid molecule comprising contacting the nucleic acid molecule with any prokaryotic DNA repair ligase polypeptide. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of modifications of nucleic acid molecules and DNA repair ligase polypeptides broadly encompassed by the claims. The claims rejected under this

section of U.S.C. 112, first paragraph, do not specify the type of nucleic acid modification encompassed by the claims nor do the claims place any structural limits on the polypeptides of the claimed methods. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to those methods of ligating nucleic acid molecule ends comprising contacting that ligase isolated from *Mycobacterium tuberculosis* and having the amino acid sequence of database accession number CAB08492 with the nucleic acid ends under the appropriate conditions.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications of any nucleic acid molecule comprising the use of any prokaryotic DNA repair ligase polypeptide because the specification does not establish: (A) the nature of the nucleic acid molecule modification claimed and the relationship to such modifications to specific polypeptides, (B) regions of prokaryotic DNA repair ligase polypeptide which may be modified without effecting the desired activity; (C) the general tolerance of prokaryotic DNA repair ligase polypeptides to modification and extent of such tolerance; (D) a rational and predictable scheme for modifying any amino acid residue of a prokaryotic DNA repair ligase polypeptides with an expectation of obtaining the desired biological function; and (E) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain the activity necessary to practice the method claimed and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those methods of the claimed genus.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any number of nucleic acid modifications

comprising the use of any prokaryotic DNA repair ligase polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of those methods and required polypeptides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 102(b) as being anticipated by Mahajan et al. (U.S. Patent No. 5,976,806) as evidenced by Srivastava et al. (Journal of Biological Chemistry, Vol. 280, No. 34, pp 30273-30281, 2005).

Mahajan et al. teach method of modifying a nucleic acid molecule comprising: contacting the nucleic acid molecule with a prokaryotic DNA ligase polypeptide. The method taught by Mahajan et al. involves prokaryotic DNA ligases from *E. coli* and *Thermus aquaticus*, each of which comprise a ligase domain which shares greater than 20% sequence identity with a/the corresponding domain sequence of Mt-Lig (CAB09492). The evidence of the sharing of greater than 20% sequence identity

between the ligase domain in E. coli and the corresponding domain in Mt-Lig is based upon the reference Srivastava et al. who teaches the crystal structure of DNA ligase from Mycobacterium tuberculosis and the identification of inhibitors of the Mt Lig. Srivastava et al. further teaches that the identified inhibitors of Mt-Lig also inhibit DNA ligase from E. coli, "most likely due to the conserved nature of the binding site of this class of enzyme" (page 30280, right column, last line of second to last paragraph). It is realized that the reference Srivistava et al. is not available as prior art, however, Srivastava et al. is only being used to evidence that the E. coli ligase has greater than 20% sequence identity to the Mt-ligase.

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G. Hutson whose telephone number is 571-272-0930. The examiner can normally be reached on M-F, 7:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Nashaat T. Nashed can be reached on 571-272-0934. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

rgh
5/20/2009

/Richard G Hutson/
Primary Examiner, Art Unit 1652